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Red Hair, Light Skin, and UV-Independent Risk for Melanoma Development in Humans

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A key gene that regulates pigmentation in humans is the melanocortin-1-receptor gene (*MC1R*; OMIM 155555), which encodes a 7-transmembrane G-protein–coupled receptor that regulates adenosine 3′, 5′ cyclic monophosphate (cAMP) levels in melanocytes. *MC1R* is activated by melanocyte stimulating hormone (MSH), which is secreted by UV-irradiated keratinocytes in the "tanning" response.[1] *MC1R* loss of function is one means of generating light skin that likely facilitates vitamin D biosynthesis. This plausibly provided an evolutionary selective advantage in preventing lethal vitamin D deficiency at high latitudes. Negative selective pressure may have arisen at low latitudes (higher UV intensity) owing to photolysis of vital factors such as folate or potentially increased skin cancer risk in lightly pigmented individuals.

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In individuals with Fitzpatrick skin type 1, light skin, and red hair, more than 80% bear a dysfunctional variant in both *MC1R* alleles.[2] *MC1R* signaling upregulates tyrosinase, the strong enzymatic activity of which results in synthesis of brown-black eumelanin. In contrast, loss-of-function *MC1R* variants produce lower cAMP and tyrosinase levels, which induce formation of pheomelanin pigment. Pheomelanin not only lacks efficient UV shielding capacity, but it (or its biosynthetic intermediates) actively induces formation of reactive oxygen species (ROS) as well as DNA damage.[3] About 60% of persons with skin type 2 carry a single loss-of-function *MC1R* allele, while fewer than 20% of all individuals with skin type 3 or higher show 1 dysfunctional allele.[2]

Melanoma incidence has risen over 30-fold in the last century.[4] Among individuals of European descent in the United States, melanoma incidence is about 3 times higher than in Asians and about 15 times higher than in individuals from South America and Africa.[5] Because melanin levels largely influence melanoma risk, studies have examined the effect of yellow-red pheomelanin and brown-black eumelanin on this melanoma risk.[6]

While UV is a key contributor to melanoma risk, with numerous UV signature mutations typically found throughout the melanoma genome, certain studies have suggested that additional mechanisms may contribute to melanoma risk. One of the suggested contributors is pheomelanin. In a preclinical model, Mitra and colleagues[7] studied mice carrying a conditional allele of *BRAF* V600E that on a genetically black background (wild-type *Mc1r*) produces benign nevi. When it was crossed onto an *Mc1r* loss-of-function background, about 50% of mice developed invasive melanomas. To investigate whether the melanoma risk was related to the pheomelanin pigment in the *Mc1r* loss-of-function gene (or a different biological consequence of having low cAMP signaling), the researchers crossed a tyrosinase mutant allele (albinism) onto the red-*Mc1r*–mutant *BRAF* V600E background and found that the melanoma risk was eliminated. This study suggests that pheomelanin, or the pathway downstream of tyrosinase that is responsible for pheomelanin synthesis, contributes substantially to melanoma risk in this UV-independent genetically defined system.[7]

In the absence of UV exposure, the skin of these red-haired mice also contained significantly increased lipid peroxidation and oxidative DNA damage compared with the skin from genetically matched albino-red animals. Recognition of pheomelanin and oxidative stress as UV-independent drivers of murine melanoma formation raised the question of how important this effect might be in humans. An intrinsic challenge to defining a UV-independent role of pheomelanin in human melanoma arises from difficulties in controlling for UV exposure among patients with melanoma.

In this issue of *JAMA Dermatology*, Wendt et al[8] report a case-control study that addresses this challenge. They investigate the effect of *MC1R* variants on melanoma formation in UV-dependent and UV-independent contexts in 991 patients with melanoma and 800 control participants and find that individuals carrying 2 *MC1R* variants were at higher risk of melanoma than wild-type carriers, independent of UV exposure.

Patients were stratified according to their *MC1R* mutation status, and 5 high-risk variants ("R," complete loss of function: Ins86_87A, R142H, R151C, R160W, and 146 D294H) and 5 low-risk variants ("r," partial loss of function: V60L, D84E, V92M, I155T, and R163Q) were genotyped. Adjustment for age and sex confirmed that more than 12 sunburns in life, 10 or more sunburns before age 20 years, and severe signs of actinic skin damage were associated with significantly increased melanoma risk. And melanoma risk increased with the number of *MC1R* variants: in this UV-dependent, but age- and sex-independent context, single-variant carriers had 1.35-fold (95% CI, 1.05-1.73; $P = .02$) to 1.94-fold (95% CI, 1.45-2.60; $P < .001$) increased risk compared with wild-type carriers; those with 2 or more variants had a greater than 2-fold higher risk (odds ratio [OR], 2.13; 95% CI, 1.66-2.75; $P < .001$).

To investigate UV-independent effects, the analysis was adjusted not only for age and sex but also for variables related to sun exposure, such as a history of sunburns in childhood and adolescence, as well as clinically visible signs of actinic sun damage. This adjustment revealed a significant correlation between melanoma risk and *MC1R* variant status, resulting in a 1.5-fold (95% CI, 1.01-2.21; $P = .04$) to 2.63-fold (95% CI, 1.82-3.81; $P < .001$) melanoma risk increase. Overall, this carefully performed study indicates that individuals carrying *MC1R* variants display a UV-independent significant intrinsic risk, highlighting a need to better understand how *MC1R* variants, pheomelanin, and ROS affect melanoma development and how to protect these individuals at elevated risk.

Morgan and colleagues[9] propose a concept in which pheomelanin might either reduce or consume major antioxidants or increase ROS generation directly. Panzella and colleagues[10] studied how pheomelanin, originating from human red hair, affects the cellular redox system and autoxidation of reduced glutathione (GSH), a major cellular antioxidant, and found that both GSH and nicotinamide adenine dinucleotide (NADH) levels were significantly diminished by pheomelanin.[10] The question of whether *MC1R* may also control various redox genes, like 8-oxoguanine DNA glycosylase and the apurinic apyrimidinic endonuclease 1,[11] or might influence lipid peroxidation via pheomelanin-metal complexes[12] has not yet been fully clarified.

Given the known danger originating from excessive cutaneous ROS, the question of how to protect individuals from an elevated intrinsic melanoma risk arises. Clearly, the correct and continuous application of UV-filter sunscreen reduces melanoma formation and limits additional UV-induced ROS exposure as well as other UV-mediated carcinogenic events. As demonstrated in a large-scale carefully conducted randomized controlled trial in Australia,[13] sunscreen application significantly reduces melanoma formation, by about 50%. In *braf* V600E mice, a broad-spectrum sun filter delayed the onset of UV-induced melanomas, offering partial protection.[14] Although these studies strongly support efforts made in public health promotions encouraging use of sunscreens, currently available sun filters and prevention recommendations might not fully cover additional intrinsic risk factors, such as those associated with UV-independent pheomelanin-related chemistry.

Because UV-A radiation, a major ROS inducer, likely plays an important role in melanoma formation, sunscreen manufacturers are seeking to incorporate ingredients that broadly filter both UV-A and UV-B. However, about half of all sun filters promoted as "broad spectrum" protection exhibited only low or medium protection from UV-A.[15] Therefore, implementation of stricter guidelines and extra sun care actions, such as physical sun protection and sun avoidance, must still be emphasized.

Carrying the findings of Wendt et al[8] further, we may find it valuable to consider whether UV-independent (pheomelanin-related) carcinogenic risk might occur in light-skinned non-red-haired individuals. While red-haired individuals usually carry *MC1R* red hair–variant alleles, it is possible that other individuals with light skin (eg, Fitzpatrick phototype 2) may harbor related chemical events within their skin, perhaps to a lesser degree. The finding by Wendt et al is also consistent with the observation that melanoma is more likely to occur on non-sun-exposed anatomic locations of lightly pigmented individuals compared with nonmelanoma skin cancers (which are more tightly linked to UV).

One controversial preventive strategy might be to use antioxidants within sun filters. While antioxidants might produce direct antagonistic chemical activities against pheomelanin-associated ROS generation, several studies have demonstrated worsening behavior of various cancers, including melanoma,[16] following use of the thiol antioxidant *N*-acetyl cysteine. It is possible that such antioxidants are inadvertently protecting existing malignant (or premalignant) cell clones from oxidative stress intrinsic to malignant transformation. If so, then it may be difficult—and hazardous—to use antioxidants as a preventive measure. Such "shotgun" approaches seem ill-advised given our current understanding of the underlying chemistry. However, it may be valuable to better understand which precise prooxidant and antioxidant species are involved and how the skin's intrinsic antioxidant defenses work and to consider the role(s) of cutaneous pigments (especially dark brown-black eumelanin).

There are likely to be valuable lessons available to learn from nature, since humans with dark skin pigmentation or easy tanning capacity exhibit profoundly lower risk of both melanoma and nonmelanoma skin cancers. This lower risk occurs despite the relatively weak sun protection factor value of eumelanin. Perhaps dark pigment is a more optimal antioxidant species that does not exert a survival benefit to premalignant cells. However, the use of UV irradiation to produce dark pigmentation would clearly be a suboptimal and hazardous strategy.

The study by Wendt and colleagues[8] provides valuable insight into a silent UV-independent melanoma risk that has no clear current preventive strategy. For now, lightly pigmented individuals need to understand the risks associated with sun exposure and should use physical sun protection whenever possible. Regular skin examination and thorough self-examination remain valuable steps toward halting melanoma mortality.

ARTICLE INFORMATION

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REFERENCES

1. Cui R, Widlund HR, Feige E, et al. Central role of p53 in the suntan response and pathologic hyperpigmentation. *Cell*. 2007;128(5):853-864.

2. Valverde P, Healy E, Jackson I, Rees JL, Thody AJ. Variants of the melanocyte-stimulating hormone receptor gene are associated with red hair and fair skin in humans. *Nat Genet*. 1995;11(3):328-330.

3. Lin JY, Fisher DE. Melanocyte biology and skin pigmentation. *Nature*. 2007;445(7130):843-850.

4. D'Orazio JA, Nobuhisa T, Cui R, et al. Topical drug rescue strategy and skin protection based on the role of Mc1r in UV-induced tanning. *Nature*. 2006;443(7109):340-344.

5. American Cancer Society. Index page. http://www.cancer.org/index. Accessed February 26, 2016.

6. Greco G, Panzella L, Verotta L, d'Ischia M, Napolitano A. Uncovering the structure of human red hair pheomelanin: benzothiazolylthiazinodihydroisoquinolines as key building blocks. *J Nat Prod*. 2011;74(4):675-682.

7. Mitra D, Luo X, Morgan A, et al. An ultraviolet-radiation-independent pathway to melanoma carcinogenesis in the red hair/fair skin background. *Nature*. 2012;491(7424):449-453.

8. Wendt J, Rauscher S, Burgstaller-Muehlbacher S, et al. Human determinants and the role of melanocortin-1 receptor variants in melanoma risk independent of UV radiation exposure [published online April 6, 2016]. *JAMA Dermatol*. doi:10.1001/jamadermatol.2016.0050.

9. Morgan AM, Lo J, Fisher DE. How does pheomelanin synthesis contribute to melanomagenesis?: Two distinct mechanisms could explain the carcinogenicity of pheomelanin synthesis. *Bioessays*. 2013;35(8):672-676.

10. Panzella L, Leone L, Greco G, et al. Red human hair pheomelanin is a potent pro-oxidant mediating UV-independent contributory mechanisms of melanomagenesis. *Pigment Cell Melanoma Res*. 2014;27(2):244-252.

11. Kadekaro AL, Chen J, Yang J, et al. Alpha-melanocyte-stimulating hormone suppresses oxidative stress through a p53-mediated signaling pathway in human melanocytes. *Mol Cancer Res*. 2012;10(6):778-786.

12. Krol ES, Liebler DC. Photoprotective actions of natural and synthetic melanins. *Chem Res Toxicol*. 1998;11(12):1434-1440.

13. Green AC, Williams GM, Logan V, Strutton GM. Reduced melanoma after regular sunscreen use: randomized trial follow-up. *J Clin Oncol*. 2011;29(3):257-263.

14. Viros A, Sanchez-Laorden B, Pedersen M, et al. Ultraviolet radiation accelerates BRAF-driven melanomagenesis by targeting TP53. *Nature*. 2014;511(7510):478-482.

15. Environmental Working Group. US Sunscreens Get Flunking Grade For UVA Protection. http://www.ewg.org/release/Sunscreens-Get-Flunking-Grade-for-UVA-Protection. Accessed January 9, 2016.

16. Piskounova E, Agathocleous M, Murphy MM, et al. Oxidative stress inhibits distant metastasis by human melanoma cells. *Nature*. 2015;527(7577):186-191.

Psoriasis, Type 2 Diabetes Mellitus, and Obesity
Weighing the Evidence

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Psoriasis is a common, chronic inflammatory disease that is associated with an increased risk of cardiovascular, metabolic, and renal disease in a manner that varies with the severity of psoriasis and is often independent of traditional risk factors for these other diseases.[1,2] The clinical significance of these associations is emphasized by premature death, particularly in patients with more severe psoriasis, in whom excess mortality is comparable to that seen in rheumatoid arthritis treated with disease-modifying medications.[3] The association of psoriasis with type 2 diabetes mellitus and obesity has been extensively studied and has been the subject of numerous meta-analyses that clearly establish an association of psoriasis with both obesity and diabetes.

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Lønnberg and colleagues[4] have provided new insights into these associations by studying monozygotic and dizygotic twins with and without psoriasis. Their main findings were that psoriasis is associated with diabetes independent of sex, age, smoking, and body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) (odds ratio, 1.53; 95% CI, 1.03 to 2.27) and that increases in BMI are associated with increasing odds of twins reporting a diagnosis of psoriasis. Similar findings were reported for hospitalized patients in whom psoriasis was diagnosed. The unique twin design of the study by Lønnberg and colleagues, in which an increasing BMI was associated with a diagnosis of psoriasis, allowed the investigators to identify a genetic correlation between psoriasis and BMI of 0.12 (95% CI, 0.08 to 0.19). A genetic correlation of similar magnitude of psoriasis and type 2 diabetes of 0.13 (95% CI, −0.06 to 0.31) was also observed, but this finding was not statistically significant (the prevalence of diabetes in this sample was quite low, yielding only 6 patients with psoriasis who also had diabetes). The magnitude of the genetic correlation is modest and similar to what has been reported for age at menarche and type 2 diabetes (−0.13).[5] Nevertheless, these findings are consistent with emerging genetic evidence linking psoriasis to diabetes. For example, genetic variation in *IL12B*, *IL23R*, and *IL23A* has an influence not only on the risk for psoriasis but also on its severity and type 2 diabetes.[6] Other researchers have suggested a role for *CDKAL1* in conferring susceptibility to both psoriasis and diabetes.[7]

Only a few studies have examined the incidence (risk) of diabetes in patients with psoriasis while adjusting for major confounding variables (eg, BMI and hypertension), and only a subset of these were able to evaluate effects of the severity of psoriasis on the association of diabetes with psoriasis (using treatment patterns).[8] The results of these studies suggest that psoriasis is associated with an increased risk of diabetes independent of major risk factors in a manner that correlates with the severity of psoriasis. Although the design used by Lønnberg et al[4] does not address diabetes risk (ie, incidence) or directly evaluate a dose-response association of the severity of psoriasis to diabetes, its careful control for BMI, which most large population-based studies are unable to capture, adds to the weight of evidence suggesting psoriasis as a risk factor for diabetes. Additional population-based studies have similarly noted an increased prevalence of insulin resistance in patients with psoriasis in a manner that varies positively with increasing body surface area affected by psoriasis and independent of major risk factors such as BMI, hypertension, and dyslipidemia.[9]

Although inflammation is often invoked as a mechanistic link to insulin resistance, a simultaneous analysis of patients with psoriasis and rheumatoid arthritis with adjustment for major risk factors demonstrated an increased risk for diabe-